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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/021,753	10/30/2001	Ken Fujise	UTSH:251US	6306

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 03/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/021,753	FUJISE ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-88* is/are pending in the application.

4a) Of the above claim(s) *1-38 and 48-62* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39-47 and 63-88* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

This Action is in response to the communication filed on 11/26/04. The amendment filed 11/26/04 is acknowledged. The amendment has been entered. Claims 1-88 are currently pending in the application and are addressed herein.

Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments. The Examiner's response to Applicant's arguments can be found after all rejections, at the end of this Action.

Election/Restrictions

Claims 1-38 and 48-62 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected Invention, there being no allowable generic or linking claim as indicated in a previous Office Action. Election was made **without** traverse in the reply filed on 6/1/2004.

Claims 39-47 and 63-88 are examined herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39-47, 63-83 and new claims 84-87 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection was set forth in the previous Office Action and is reiterated below, for convenience.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (See MPEP 2100-164)

In the instant case, the claims encompass methods for identifying modulators of "a Fortilin polypeptide" (see claims 39 and 68). The phrase "a Fortilin polypeptide" implies that there is more than one Fortilin polypeptide (se p. 10, lines 24-26). Looking to the specification for guidance, it is clear that term "a Fortilin polypeptide" encompasses variants of Fortilin, such as the possible variants described on pages 26-30 of the specification, including "biologically functional equivalents" of Fortilin which are described as variants of Fortilin that maintain the biological function of Fortilin (see p. 27, lines 15-20).

Therefore, the instant claims encompass methods wherein the methods utilize "a Fortilin polypeptide" wherein the Fortilin polypeptide could be any variant of Fortilin that maintains the biological activity of Fortilin. As such, the claims are drawn to the use of a molecule wherein the molecule can be any one species of huge genus of Fortilin variants. The specification has only described one species of this vast genus—the wild-type Fortilin polypeptide disclosed as

SEQ ID NO: 2. The specification does not disclose any other variants of Fortilin that maintain Fortilin activity, nor does the specification indicate which amino acids of Fortilin can be changed or deleted and result in a "biologically active" Fortilin variant. Furthermore, there is no structure function relationship described such that one of skill in the art would be able to clearly recognize any critical structural elements of Fortilin. Considering the huge number of possible variants encompassed by the claims and the limited guidance provided in the specification with respect to identifying the biologically active variants encompassed by the claims, it is the Examiner's position that the specification has not adequately described a sufficient number of "representative species" encompassed by the claims, as required.

It is noted that the specification does has proper written description disclosure of the human fortilin polypeptide (but no variants thereof).

Additionally, claims 39-47, 63-83 new claims 84-87 are also rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, in view of the written description rejection above. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As mentioned above, the claims encompass Fortilin variants for which there is insufficient written description provided in the specification. Without a clear description of the biologically active Fortilin variants encompassed by the claims one of skill in the art would not know how to make and use the claimed invention without performing an undue amount of additional experimentation.

It is noted that the specification has disclosed a method for identifying inhibitors of p53-Fortilin interaction (using human Fortilin, but not variants thereof) in an in vitro assay, as specifically described in Example 9 on page 159 of the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 68-83 and 85-87 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection. This rejection is necessitated by the amendment to claim 68.**

37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

MPEP §2163.06 notes:

If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).

MPEP §2163.02 teaches that:

Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was

filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.

MPEP §2163.06 further notes:

When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure.

The instant claims are drawn to:

A method of identifying a modulator of a Fortilin polypeptide comprising:

(a) contacting a candidate modulator with a recombinant cell expressing the Fortilin polypeptide;

(b) measuring the level of Fortilin activity or expression of the cell; and,

(c) comparing the level of Fortilin activity or expression of the cell to the level of Fortilin activity or expression of a cell not contacted with the candidate modulator,

wherein a difference between the level of Fortilin activity or expression indicates that the candidate modulator is a modulator of a Fortilin polypeptide.

It is noted that claim 68 has been amended such that the claim is now limited to a method of identifying a modulator of a Fortilin polypeptide using a recombinant cell expressing the Fortilin polypeptide. It is noted that claim 68 is not limited to a recombinant cell that that has been transfected with a nucleic acid that encodes and expresses Fortilin. In fact, the claim language is broad and encompasses using a cell that has been transformed with anything wherein the cell expresses an endogenous Fortilin polypeptide.

Applicants have indicated that support for the amendment can be found in Example 9, pages 159-160 of the specification (see page 17 of the response filed 11/26/04).

Looking to the specification it is noted that with respect to a method using a recombinant cell for identifying compounds that "modulate a Fortilin polypeptide", Example 9, pages 159-160 discloses, under the title "Identification of inhibitors of p53 Fortilin Interaction"

> "[A] stable transfection will be established in mammalian cells. These cells will have stably transfected plasmids: i) A plasmid to produce the GALA-DNA-BD (binding domain)-Fortilin; ii) A plasmid to produce the VPI6-DNA-AD (activating domain)-ps3; and iii) A reporter plasmid that contain beta-galactosidase reporter gene under the control of a GAL4-responsive element and the minimal promoter of the adenovirus Elb.
>
> The transfected cells will be seeded on 96 well plates. Candidate compounds will be dissolved in PBS (pH=7.4), added to the media, and incubated before cells are assayed for β-galactosidase activity. The lower the activity of β-galactosidase, the higher the inhibitory effect of the candidate compound."

Therefore, the Example 9 does not disclose a method of identifying a modulator of a Fortilin polypeptide using a recombinant cell expressing the Fortilin polypeptide. Example 9 does disclose a method of identifying an inhibitor of p53-Fortilin interaction, using a cell transfected with specific plasmids. Therefore, Example 9 is not commensurate in scope with the instant claims and thus does not provide the proper support required for the instant claims.

The Examiner has thoroughly searched the specification for support for the instant claims. The following disclosure was found in the specification: Example 12, (p. 161), cell line cells (in vitro) were stably transfected with a plasmid to expresses HA-Fortilin and interaction of the HA-Fortilin with p53 was assayed. Examples 13 and 15 (p. 162 and 163) a cell line cell (in vitro) was stably transfected to express Fortilin and Apoptotic activity in the cells were assayed. Example 14 (p. 162-163) a cell line cell (in vitro) was stably transfected to express Fortilin and

Caspase-3-like activity was assayed in the cells. Example 15 (p. 163-164) cell line cells (in vitro) were transfected with a plasmid that expressed antisense-Fortilin polynucleotide and a plasmid expressing a reporter gene to determine anti-apoptotic activity of Fortilin. Example 16 (p. 164) cells were stably transfected (in vitro) with a plasmid that expressed HA-Fortilin and localization of Fortilin was determined. Also, Examples 17-22 (pp. 164-168) all encompassed stably transfecting cells (in vitro) with a polynucleotide that expresses a Fortilin polypeptide. It is noted that Examples 12-22 do not disclose methods for identifying modulators of Fortilin activity.

The only Example found in the specification that specifically discloses a method of identifying compound that affects Fortilin activity is the disclosure in Example 9 which is specifically drawn to identifying inhibitors of p53-Fortilin interaction using a cell (in vitro) stably transfected with the 3 plasmids indicated and performing the specific assay to determine if the candidate inhibits p53-Fortilin interaction.

It is noted that the specification (specifically, Example 9) does have support for a method of identifying an inhibitor of p53-Fortilin interaction using an in vitro recombinant cell that has been stably transfected with i) a plasmid to produce the GALA-DNA-BD (binding domain)-Fortilin; ii) a plasmid to produce the VPI6-DNA-AD (activating domain)-ps3; and iii) a reporter plasmid that contain beta-galactosidase reporter gene under the control of a GAL4-responsive element and the minimal promoter of the adenovirus Elb wherein the candidate inhibitor is contacted with the recombinant cell and beta-galactosidase activity is assayed wherein the lower the activity of β-galactosidase (compared to a proper control cell), the higher the inhibitory effect of the candidate compound.

It is noted, however, that the specification does not appear to have support for a method of identifying a modulator of Fortilin activity using a transfected cell that expresses Fortilin as claimed.

Since proper support for amended claim 68 cannot be identified in the specification, the instant rejection is appropriate.

Response to Arguments

Applicants arguments filed 11/26/04 has been fully considered.

The rejection of claims under 35 USC 12, first paragraph written description and enablement are based on the lack of sufficient written support for the claimed genus of Fortilin polypeptides encompassed by the claims. Therefore, Applicants arguments with respect to both rejections are addressed together.

Applicants argue that the specification discloses human Fortilin amino acid sequence and compares it to similar sequences in 7 other species or organisms ranging from yeast, rice, insects and chicken to other mammals (Figure 1A). Applicants indicate that that the human and mouse sequences are 95% identical and human and insect are identical in 85 of 172 amino acids (49%). Applicants assert that it is well known that conserved residues of a protein are considered to be important, and the conserved amino acids that make up half the amino acid sequence of Fortilin are expected to be important for function (See p. 19, second paragraph). Applicants also contend that many of the amino acid residues that are not conserved are similar in nature, indicating that these amino acids are also important for function. Applicants contend that based on the indicated sequence alignment, a person of skill in the art would recognize that Fortilin variants retaining

biological activity could be prepared by changing Fortilin amino acids at variant residues while keeping the conserved residues intact. It is asserted that this can be accomplished, for example, by replacing a variant residue with a chemically similar residue, or by replacing a variant residue of one Fortilin sequence (i.e., human) with the corresponding amino acid residue found in the Fortilin sequence of a different species (i.e., mouse). Furthermore, Applicants contend that the specification discloses methods to assay Fortilin activity (see p. 20).

In sum, Applicants contend:

> "In sum, the specification describes and identifies the position of physically conserved residues, functionally conserved residues, and variable residues of the Fortilin sequence. Those of skill in the art would recognize that biologically active Fortilin variants are those that have amino acid changes at the variable positions of the protein. This, plus the ability to determine the activity of Fortilin variants by assays described in the specification, provides sufficient guidance to identify and generate biologically active Fortilin variants.
> The specification teaches the structure of biologically active Fortilin variants and correlates structure with function for conserved residues of the protein. In doing so, these teachings provide more than enough identifying characteristics of Fortilin variants to show that Applicants were in possession of the claimed Fortilin polypeptides. As such, claims 39-47 and 63-83 satisfy the written description requirement." (See p. 20).

In response, first, it is noted that Applicants acknowledge that the claims encompass Fortilin polypeptides, including Fortilin variants (see p. 18, third paragraph). With respect to the sequence alignment of human Fortilin with the polypeptides of the other various species of organisms, it is noted that the other sequences are disclosed as "Fortilin" polypeptides based solely on the indicated sequence alignment.

Contrary to Applicants assertion "The specification teaches the structure of biologically active Fortilin variants and correlates structure with function for conserved residues of the protein" there is no disclosure in the specification or that has been found in the prior art which

indicates the activity/function of any of the disclosed "Fortilin" polypeptides of non-human species. Therefore, it is not clear if the "Fortilin" polypeptides disclosed have the same function as human Fortilin. Since the non-human "Fortilin" polypeptides are not disclosed as having the same function, identifying conserved "functional domains" based on sequence alignment alone is tenuous at best, and would certainly require additional experimentation to determine the function of the non-human polypeptides and yet further experimentation to determine if the "conserved regions" are actual biologically active functional domains that confer the same function.

Additionally, the art recognizes that although structural similarity can serve to classify a protein as related to other known proteins, this classification is insufficient to establish a function or biological significance for the protein because ancient duplications and rearrangements of protein-coding segments have resulted in complex gene family relationships. Duplications can be tandem or dispersed and can involve entire coding regions or modules that correspond to folded protein domains. As a result, gene products may acquire new specificities, altered recognition properties, or modified functions. Extreme proliferation of some families within an organism, perhaps at the expense of other families, may correspond to functional innovations during evolution. See **Henikoff et al. (Science 1997; page 609, Abstract)**. Accordingly, one skilled in the art would not accept mere homology as establishing a function of protein because gene products may acquire new specificities, altered recognition properties, or modified functions. Rather, homology complements experimental data accumulated for the homologous protein in understanding the homologous protein's biological role. Although, the presence of a protein module in a protein of interest adds potential insight into its function and guides experiments, insight into the biological function of a protein cannot be automated. However,

homology can be used to guide further research. (See Henikoff, paragraph bridging pages 613-614, through page 614, paragraph bridging columns 1-2).

Furthermore, the art recognizes that a high degree of structural homology may not result in functional homology. **Witkowski** et al. (Biochemistry 38:11643-11650, 1999) teaches that one amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. **Seffernick** et al. (J. Bacteriol. 183(8):2405-2410, 2001) teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Therefore, the claimed genera of "Fortilin" polypeptides have the potentiality of having many different functions.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). For the reasons indicated in the rejection, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of Fortilin polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, the claims encompass a genus of "Fortilin" polypeptides that includes variants of human Fortilin which are structurally (and possibly functionally) different from those explicitly described in the specification. The claimed genus encompasses all possible "Fortilin" polypeptide variants (a huge number of possibilities), however, the specification has not adequately described a sufficient number of species or the critical functional elements common to the members of the genus. Therefore, the written description requirement has not been met and the rejection is proper.

The amendment to the specification has overcome the objections to the specification. Therefore, the objections to the specification have been withdrawn.

The amendment to the claim has obviated the rejection under 35 USC 112, second paragraph. As such the rejection is withdrawn

Applicants' arguments with respect to the art rejections are persuasive. Therefore, the rejection of claims under 35 USC 102 has been withdrawn.

It is noted that the amendment to claim 68 has necessitated the new grounds of rejection set forth above. Therefore, it is proper to make this rejection FINAL.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

DAVE TRONG NGUYEN
PRIMARY EXAMINER

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Art Unit 1635